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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,093	06/14/2001	Catherine Guenther	R-126	7936

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,093	GUENTHER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-52* is/are pending in the application.

4a) Of the above claim(s) *51 in part* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-50 52, all, and 51, in part,* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 have been canceled. Claims 39-52 have been added.

Applicant's arguments filed 3-22-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 39-52 are under consideration as they relate to a transgenic mouse having a disruption in a mCAR gene, a cell isolated from the mouse, and a method of identifying an agent using the mouse.

Newly submitted claim 51 encompasses an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims as originally filed did not include "tissue" isolated from a mouse having a disruption as claimed. Such tissue would be patentably distinct from cells because the cells are used for in vitro assays while tissues are used for transplantation.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims' 51 tissue embodiments are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

The objection to claim 10 is withdrawn because it has been canceled.

Specification

The amendment to the description of Fig. 2A-2B on pg 8 has been entered. The description of Fig. 2 is now clear.

The application numbers throughout the specification will require updating as necessary.

Claim Rejections - 35 USC § 101

Claims 39-52 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for reasons of record.

Claims 39-50 are directed toward a transgenic animal having a disruption of a nuclear hormone receptor gene. Claim 52 is directed toward using such a transgenic animal to test agents. The specification teaches making mice having a homozygous disruption in the nuclear hormone receptor of SEQ ID NO:1 (pg 51). The specification suggests using the mice as a model of disease, specifically as a model for infertility, glucose metabolism, diabetes, behavioral, neurological, neuropsychological, psychotic phenotypes (pg 18-20; pg 20, line 2). However, the specification does not disclose that neurological, neuropsychological or psychotic disease found in humans is linked to a disruption in the nuclear hormone receptor of SEQ ID NO:1. The mice had abnormalities in the spleen, thymus and lymph nodes (pg 52-53); however, the specification does not teach how to use such mice as a model of disease. The mice showed decreased performance in the rotarod test. However, the specification does not teach how to use such mice as a model of any disease or that a disruption in SEQ ID

NO:1 in humans relates to a disease that causes decreased coordination. None of the phenotypes found by the tests correlate to a useful phenotype because the phenotypes described are not specific to a disease and are not linked to a disruption in the human equivalent of SEQ ID NO:1. The results of the behavioral tests are also not statistically significant because the number of mice tested is not disclosed. The mice claimed cannot be used to determine compounds that modulate nuclear hormone receptor expression because nuclear hormone receptor is not expressed in the cells of the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that ameliorate any condition using the mice. Thus, the specification does not provide a specific or substantial use for a mouse as claimed, specifically having the phenotypes recited in claims 17-29.

Claim 51 directed toward cells derived from the transgenic animal is included because the cells lack a specific and substantial utility for the reasons above, because the specification does not teach how to use the cells other than when they are part of a mouse that is a model of disease and because the specification does not teach how to make the cells in the absence of the mouse.

Applicants point out the application teaches making the mouse having the phenotype claimed and asserts numerous utilities for the mice. Applicants' arguments are not persuasive. None of the asserted utilities are substantial, credible and specific.

Applicants point out the asserted utility of using the mice claimed for conditions associated with impaired coordination or balance, or organ abnormalities (pg 19, lines 6-16 and 23-27). Applicants are the skilled artisan would be able to use the mice to develop treatments that ameliorate these conditions. Applicants' arguments are not persuasive.

The medical profession does not treat organs having decreased size or weight; therefore, treating organ size or weight is not a substantial or credible utility. Nor are organs having decreased size or weight specific to any disease; therefore, treating organ size is not a specific utility.

The medical profession does not treat organ to body weight ratio; therefore, treating organ to body weight ratio is not a substantial or credible utility. Nor is organ to body weight ratio specific to any disease; therefore, treating organ to body weight ratio is not a specific utility.

The medical profession does not treat spleens, thymuses or lymph nodes having lymphoid depletion; therefore, treating spleens, thymuses or lymph nodes having lymphoid depletion is not a substantial or credible utility. Nor are spleens, thymuses or lymph nodes having lymphoid depletion specific to any disease; therefore, treating organ size is not a specific utility. While patients having decreased lymphoid cells are treated as a whole, the spleens, thymuses and lymph nodes are not specifically treated; therefore, targeting the increase of lymphoid cells to spleens, thymuses or lymph nodes is not credible.

The asserted utilities for a mouse having impaired coordination are not specific, substantial or credible. First, the medical profession does not specifically treat impaired coordination. For example, impaired coordination in the elderly may occur and may be caused by osteoporotic bones, symptoms of pain, or atrophied muscles. The osteoporotic bones, symptoms of pain or atrophied muscles would be treated, not the impaired coordination. Furthermore, "impaired coordination" is a relative term. Second, the medical profession does not treat clumsiness. For example, a first tennis player may have impaired coordination, or lower than average coordination (clumsy), while the second tennis player has better than average coordination. The specification does not teach how to treat the first player so that the first player would be as coordinated as the second player. Treating clumsiness cannot be envisioned; therefore, using the mouse as a model for clumsiness is not a substantial or credible utility. In addition, the rotarod test used to determine impaired coordination is used to test gross neurological function; therefore, using mice with impaired coordination is not specific to any neurological condition. Overall, mice having impaired coordination do not have a specific, substantial or credible.

Applicants state the mice may be used as models of disease (impaired coordination/balance, thymus, spleen or lymph node disorders) (pg 7, lines 5-6, of response). Applicants' argument is not persuasive for reasons above. In addition, a mouse having a small or light thymus, spleen, lymph node is not specific to any disease condition. A mouse having decreased coordination/balance is not specific to any

disease. A disruption in a mCAR gene has not been linked to any disease condition. Therefore, the mice are not models of any disease.

Applicants state the mice may be used to identify agents that ameliorate disease symptoms (pg 7, line 7, of response). Applicants' argument is not persuasive. Wild-type mice could be used to determine agents that make organs bigger or heavier. Wild-type mice could be used to determine agents that improve coordination. Therefore, using mice to find agents that increase organ size/weight or coordination/balance is not specific to the mice claimed. In addition, the specification does not teach identifying any agents using the mice; therefore, applicants' assertion is not substantial.

Applicants state the mice may be used to identify agents that modulate a phenotype caused by a gene disruption (pg 7, line 8, of response). Applicants' argument is not persuasive. The specification does not describe any phenotype caused by a mCAR gene disruption in humans. The phenotypes lack utility for reasons above.

Applicants state the mice may be used to identify agents that target the mCAR (pg 7, lines 9-10, of response). Applicants' argument is not persuasive. The mice do not express mCAR, so agents that bind or target mCAR cannot be found.

Applicants states the office action suggests the only use for the claimed mouse is as a model of disease. Applicants state the office action suggests the disease being modeled must be found in humans and linked to a disruption in a mCAR gene (pg 7, 1st full ¶ of response). Applicants' statements are not true. The utility rejection is based on all the asserted utilities for the mice described on pg 18, lines 24-31, pg 1, lines 6-16 and 23-27 and pg 20, lines 7-14. One way to overcome the utility rejection is to show

that a disease condition in humans is linked to a disruption in a mCAR gene and the disease conditions are linked to the phenotype claimed. Without such links, the specificity, substantiality and credibility of the asserted utilities of the mice as models of diseases found in humans are questionable and make the basis of the rejection.

Applicants argue the mice can be used to determine the function of a gene (¶ bridging pg 7-8 of response). Applicants' argument is not persuasive. Studying the mouse to determine the function of a gene is not in and of itself a substantial utility. An invitation for using the mouse for further research to determine the function of the gene is not substantial. The function may not be determinable using the mouse. The specification does not determine the function of the mCAR gene; therefore, the assertion is also not credible.

Applicants argue that because a link between the disruption of the mCAR gene in mice and the phenotypes of impaired coordination/balance, and decreased thymus, spleen and lymph node size/weight, one of skill can now use the mice to study mice with impaired coordination/balance, and decreased thymus, spleen and lymph node size/weight (pg 8, 1st full ¶ of response). Applicants' argument is not persuasive. Treating mice with impaired coordination/balance, and decreased thymus, spleen and lymph node size/weight without a correlation to treating humans is not a "real world", substantial, credible or substantial utility.

Applicants argue no standard for statistical significance is required and the number of animals tested in the Examples need not be provided. Applicants' argument is not persuasive. The examiner is not required to provide a reference describing that it

was well known at the time of filing that those in the art used statistically significant data for scientific experiments. The statement was made by the examiner in the utility rejection to question whether the mice having the phenotypes claimed are credible. In addition, Crabbe (Science, 1999, Vol. 284, pg 1670-1672) describes the high variability in scores of different strains of mice in neurobehavioral tests and provides a p value – a measure of statistical significance (pg 1670, Table 1 caption).

Claim Rejections - 35 USC § 112

Claims 39-52 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having abnormal pain threshold for reasons of record.

The rejection regarding how to make animals or cells having a disruption in a nuclear hormone receptor gene other than mice has been withdrawn because claims 39-52 are limited to mice.

The rejection regarding obtaining a phenotype obtained in mice in other species has been withdrawn because claims 39-52 are limited to mice.

The rejection regarding providing a nexus between the disruption in nuclear hormone receptor and the phenotypes has been withdrawn in view of the limitation in claims 1 and 52 "wherein as a result of the disruption..."

The rejection regarding making or using a transgenic with a wild-type phenotype has been withdrawn because claims 1 and 52 require the mouse has impaired coordination/balance, or an abnormal thymus, spleen and lymph node.

Claims 39-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "a mCAR gene" in claim 39 is new matter. Pg 6, lines 24-29, describes a "nuclear hormone receptor gene" as being the sequence of SEQ ID NO:1 or the isoform mCAR2 in Genebank Accession No.: AF009328; GI NO: 2267577. Nowhere does the specification refer to the genus mCAR. It is unclear if mCAR is limited to mCAR2 or if other mCARs are encompassed by the term (see 112/2nd).

The phrase "tissue" in claim 51 is new matter. The specification did not contemplate tissue isolated from the mouse as claimed.

Claims 39-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection regarding the metes and bounds of "nuclear hormone receptor" has been withdrawn because the phrase is not in the new claims.

The rejection regarding "lymphoid depletion" has been withdrawn in view of new claims 44, 48 and 49 and applicants' arguments.

The rejection regarding the metes and bounds of the "periarteriolar lymphoid sheaths" has been withdrawn because claim 22 has been canceled.

The rejection regarding the metes and bounds of "consistent with" has been withdrawn because the claims have been canceled.

The metes and bounds of what applicants' consider "a mCAR gene" in new claims 39 and 52 cannot be determined. Applicants define a nuclear hormone gene on pg 6, line 24 and refer to mCAR2 but do not define the metes and bounds of a mCAR gene as claimed. The genus of mCAR is not mentioned in the specification and is not defined. Therefore, it is unclear if a mCAR gene is limited the nuclear hormone gene described on pg 6, lines 24-29. If an mCAR gene is limited to the nuclear hormone gene described on pg 6, lines 24-29, it is unclear if the gene is limited to SEQ ID NO:1 or if it encompasses SEQ ID NO:1 and the orphan nuclear hormone receptor isoform mCAR2 identified in Genebank as Accession No.: AF009328; GI NO: 2267577. Pg 6, lies 24-29, does not refer to sequences having homology to SEQ ID NO:1 as stated in the previous office action of 11-20-03. It is unclear if mCAR is limited to mCAR2 or if other mCARs are encompassed by the term.

Claim Rejections - 35 USC § 102

The rejection of claims 5-9, 11-15, 17-29 and 31-35 under 35 U.S.C. 102(b) as being anticipated by Kato (J. Biochem., May 2000, Vol. 127, pg 717-722) has been

withdrawn because the claims have been canceled. The nuclear hormone receptor gene VDR is not a mCAR gene as claimed because the nuclear hormone receptor described in the specification is limited to SEQ ID NO:1 or encompasses SEQ ID NO:1 and the orphan nuclear hormone receptor isoform mCAR2 identified in Genebank as Accession No.: AF009328; GI NO: 2267577. The nuclear hormone receptor described in the specification is not described in Kato. It is noted that the claim is not limited to the "nuclear hormone receptor" described in the specification. However, for art purposes, the phrase "mCAR gene" is being interpreted as the nuclear hormone receptor described in the specification. At most, the nuclear hormone receptor is described in the specification as encompassing SEQ ID NO:1, and mCAR2 Genbank Accession No.: AF009328; GI NO: 2267577.

Claim Rejections - 35 USC § 103

The rejection of claims 5-9, 11-15 and 31-35 under 35 U.S.C. 103(a) as being unpatentable over Capecchi (Scientific American, 1994, Vol. 270, pg 34-41) in view of Choi (J. Biol. Chem., 1997, Vol. 272, pg 23565-23571) has been withdrawn because the claims have been withdrawn and because new claims 39-52 require mice with phenotypes that could not have been predicted by one of ordinary skill in the art at the time of filing.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER